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Health and Environmental Effects Profile for Pyridine

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16. ABSTRACT

The Health and Environmental Effects Profile for Pyridine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Pyridine has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for pyridine is 0.002 mg/kg/day for inhalation exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for pyridine is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PYRIDINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3112. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Pyridine is a colorless to yellowish hygroscopic liquid with a characteristic disagreeable odor (Jori et al., 1983). It is produced in coal tar during the coking of coal (Goe, 1982; Abramovitch, 1968); however, only a small percentage of the total pyridine generated from coking operations is refined for sale. As a commercial end-product, pyridine is synthetically produced predominantly by reacting acetaldehyde, formaldehyde and ammonia (Goe, 1982). Although the most recent production figure for pyridine is 7.42 million pounds in 1968 (USTC, 1970), the estimation of current production is ~15 million pounds annually. Pyridine has the following use-pattern (Santodonato et al., 1985): agricultural chemical synthesis, 50%; piperidine synthesis, 18%; pharmaceutical use (intermediate and solvent), 10%; solvent applications, 10%; textile chemical synthesis, 2%; miscellaneous uses (mostly intermediate), 10%.

Several environmental fate processes may contribute to the removal of pyridine from the aquatic environment, with microbial degradation, perhaps, being the most important overall. Ettinger et al. (1954) observed that four different polluted river waters were able to completely biodegrade pyridine in 3-6 days with only 1-3 days required for degradation upon pyridine readdition to the waters, indicating rapid adaptation of the microbes. A number of standard biodegradation tests have demonstrated the biodegradability of pyridine, particularly after acclimation (see Table 2-1). Experimentally measured Henry's Law constants (Hawthorne et al., 1985; Hine and Mookerjee, 1975) of ~10^{-3} atm·m³/mol suggest significant, but not rapid, volatilization from environmental waters (Lyman et al., 1982), with volatilization from shallow rivers being most significant. Mill et al.

(1979, 1980) found that irradiation of natural waters containing pyridine with wavelengths >300 nm resulted in significant loss of pyridine, even though irradiation of pure water solutions of pyridine produced no degradation. Aquatic hydrolysis, oxidation by $RO_2\cdot$ or HO· radicals, adsorption, and bioaccumulation in organisms are not expected to be environmentally important.

Once exposed to the ambient atmosphere, reaction with hydroxyl radicals is expected to be the dominant chemical removal mechanism for pyridine. Based on an experimentally determined rate constant for hydroxyl radical reaction of $<1\times10^{-12}$ cm³/molecule-sec (Atkinson, 1985), a half-life >8 days can be calculated for an average atmosphere. Removal of pyridine from the atmosphere by rainfall may be possible, since it is completely water soluble. The biodegradation of pyridine by soil microorganisms has been demonstrated (Naik et al., 1972; Moore, 1949; Korosteleva et al., 1981; Watson and Cain, 1975; Shukla, 1973; Haber et al., 1983). Although experimental soil adsorption data are not available, pyridine is expected to be very mobile in soil and easily leached, based on its water solubilitiy, log K_{ow} (0.65) and chemical structure. Pyridine is expected to evaporate quite rapidly from dry surfaces based on its vapor pressure (20 mm Hg at 24.8°C).

Pyridine has been detected in wastewaters associated with shale oil processing (Pellizzari et al., 1979; Dobson et al., 1985; Hawthorne and Sievers, 1984), coal conversion processes (Singer et al., 1978), and chemical and coke manufacturing (Shackelford and Keith, 1976). These industrial and energy-related processes are probably the major source of pyridine exposure to ambient waters. Pyridine has been detected in the following components of food: the volatile flavor components of fried chicken (Tang et

al., 1983) and roasted barley (Wang et al., 1969) and waste gases from coffee roasting (Tijmensen, 1978). Sources of industrial pyridine emissions to the atmosphere include coal coking operations (Anonymous, 1979; Gracheva et al., 1983; Graedel, 1978), coffee roasting (Tijmensen, 1978), coal gasification (Lee et al., 1982), cold-box molding foundry emissions (Schandl et al., 1984), and volatilization from shale oil wastewaters (Hawthorne and Sievers, 1984). Pyridine has been identified as a component of tobacco (Schmeltz et al., 1979), cigar (Osman and Barson, 1964) and marijuana (Novotny et al., 1982) smoke.

Absorption of pyridine occurs through the respiratory and gastrointestinal tracts (Gleason et al. 1976). Gastrointestinal absorption of ^{14}C-pyridine by human volunteers was rapid and extensive (D'Souza et al., 1980). Data regarding the distribution of pyridine could not be located in the available literature as cited in the Appendix. In vivo methylation of pyridine occurs at the N-position and the chief excretory metabolite is N-methyl pyridinium hydroxide (Reinhardt and Britelli, 1981; Browning, 1965; D'Souza et al., 1980). Methylation was independent of route (oral or intraperitoneal), but decreased with increasing dose in rats and guinea pigs. Other urinary metabolites have been identified from the urine of Golden Syrian hamsters (pyridine N-oxide, 3-hydroxypyridine, 4-pyridone and 2-pyridone) (Shaker et al., 1982).

Chronic or subchronic studies on the carcinogenicity of pyridine could not be located in the available literature as cited in the Appendix. The technical report of a chronic gavage study in rats and mice is not yet available (NTP, 1985). No evidence of carcinogenicity was found in rats and mice administered pyridine in subcutaneous and intravenous studies (Mason, 1969; Mason et al., 1971; Homburger, 1968; Derse, 1969).

Pyridine was found to be nonmutagenic when tested for reverse mutation with and without metabolic activation in four strains of Salmonella typhimurium and one strain of Escherichia coli (Florin et al., 1980; Burrell et al., 1983; Riebe et al., 1982; Pai et al., 1978). Pyridine was also negative in a rec assay in E. coli (Reibe et al., 1982). Pyridine increased the frequency of SCE, but not chromosome aberrations, in Chinese hamster cells (Abe and Sasaki, 1977; Ishidate and Odashima, 1977).

One study was located on the effect of pyridine on reproduction and teratology. Landauer and Salam (1974) treated chicken eggs with 20 mg pyridine/egg at 96 hours of incubation and found muscular hyperplasia of the legs and occasional abnormalities of the facial skeleton and neck vertebrae in the chicks.

Chronic oral toxicity studies could not be located in the available literature as cited in the Appendix. Several short-term studies (Baxter, 1946, 1948; Baxter and Mason, 1947; Hove, 1953; Coulson and Brazda, 1948) have evaluated the toxicity of dietary pyridine to young rats; however, these studies were conducted for 1-4 months and many of the rats died during the first few weeks of treatment. The results consistently support a hepatotoxic effect of pyridine. Dietary concentrations of pyridine in these studies ranged from ~1000-10,000 ppm. Most rats died in the first 2-3 weeks of treatment; hepatomegaly, liver necrosis and cirrhosis, and degeneration of the renal tubular epithelium were consistently reported (Baxter, 1946, 1948; Baxter and Mason, 1947; Coulson and Brazda, 1948; Hove, 1953).

Mice treated with pyridine by gavage, 5 days/week for 13 weeks had dose-related decreased body weight gain (males) at $\geq$25 mg/kg/day and dose-related increased incidence in liver lesions, ranging from inflammation to fatty metamorphosis to necrosis at $\geq$100 mg/kg/day. Livers of mice treated at 25 or 50 mg/kg/day were not examined microscopically. Deaths occurred in 1/10

and 6/10 males treated at 200 and 400 mg/kg/day, respectively. Rats similarly treated had reduced body weight gain at ≥12.5 mg/kg/day and dose-related increased incidence in liver lesions ranging from inflammation, fibrosis and bile stasis to necrosis and cirrhosis at levels ≥50 mg/kg/day. In addition, high-dose rats had an increased incidence of interstitial myocarditis and glomerulonephritis. Death occurred in 1/10 males at 100 and 200 mg/kg/day dose levels and 2/10 females at 200 mg/kg/day.

Inhalation exposure of rats to 10 or 50 ppm (32.35 or 161.75 mg/m^3), 7 hours/day, 5 days/week for 6 months resulted in increased relative liver weight, but had no effect on growth or mortality (Encyclopedia of Occupational Safety and Health, 1983).

Toxic effects such as headaches, nervousness, sleeplessness, nausea and vomiting have been reported in humans from occupational exposure to 6-12 ppm pyridine (19-39 mg/m^3) (Teisinger, 1948). Pollock et al. (1943) reported similar symptoms in five epileptic humans given pyridine orally at 0.30-1.51 g/day. When the dosage was increased to 1.82 g/day, renal insufficiency and evidence of altered hepatic function occurred. At a dose of 2.42 g pyridine/day, death as a result of hepatorenal failure was reported. Despite the lack of adequate long-term studies, pyridine does appear to be hepatotoxic.

A provisional ADI of 0.002 mg/kg/day or 0.2 mg/day for a 70 kg human was derived from a subchronic rat inhalation LOEL using an uncertainty factor of 1000. The LOEL was associated with increased relative liver weight. The ADI is provisional pending the results of an NTP chronic gavage study in rats and mice (NTP, 1985). Also pending the results of the NTP study, pyridine was classified as an IARC Group 3 and an EPA Group D chemical. An RQ of 100 was recommended based on the findings of CNS and gastrointestinal effects in workers exposed occupationally to pyridine by Teisinger (1948).

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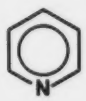
LIST OF ABBREVIATIONS

BODT	Biological oxygen demand, theoretical
CS	Composite score
DOC	Dissolved oxygen content
ICC_{50}	Concentration that inhibits culture growth by 50%
K_{OC}	Soil sorption coefficient
K_{OW}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{LO}	Lowest lethal dose
LD_{50}	Dose lethal to 50% of recipients
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOEC	No-observed-effect concentration
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
STEL	Short-term exposed level
TLV	Threshold limit value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Pyridine is the common chemical name for the compound also known by the synonyms azabenzene and azine. The chemical structure, molecular weight, empirical formula and CAS Registry number for pyridine are as follows:



Molecular weight: 79.10

Empirical formula: C_5H_5N

CAS Registry number: 110-86-1

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pyridine is a colorless (when pure), or slightly yellowish, hygroscopic liquid with a characteristic disagreeable odor and a burning taste (Jori et al., 1983; Hawley, 1981). The odor threshold in air is reported to be 0.17 ppm (Amoore and Hautala, 1983) with the odor becoming objectionable at 10 ppm (Jori et al., 1983). Pyridine is miscible with water, alcohol, ether, oils, benzene, acetone, chloroform and many other organic liquids and is a good solvent for many organic and inorganic compounds (Windholz, 1983; Hawley, 1981; Jori et al., 1983). Selected physical properties are listed below:

Freezing point:	-41.6°C	Goe, 1982
Boiling point:	115.3°C	Goe, 1982
Density at 20°C:	0.9830 g/cm³	Goe, 1982
Water solubility at 20°C:	complete	Goe, 1982
Vapor pressure mm Hg:		Perry and Green, 1984
at 2.5°C	5	
at 13.2°C	10	
at 24.8°C	20	
at 38.0°C	40	

Log K_{ow}:	0.65	Hansch and Leo, 1985
Ionization constants:		
pKa at 20°C	5.23	Albert et al., 1948
pKa at 25°C	5.22	Perrin, 1964
Vapor density:	2.73	Verschueren, 1983
Air conversion factors:	1 ppm = 3.24 mg/m³	Verschueren, 1983
Autoignition temperature:	482°C	Hawley, 1981
Flash point (closed cup):	20°C	Hawley, 1981

As a tertiary amine, pyridine reacts with various alkylating agents to form quaternary ammonium salts (Goe, 1982). It is readily reducible to the commercially important piperidine and can be oxidized by per-acid to the N-oxide derivative. Proper amination of pyridine yields 2-aminopyridine.

Pyridine is a weak base and forms salts with strong acids (Windholz, 1983). It is volatile with steam and forms azeotrophic mixtures with water. Pyridine has generally been available on the commercial market as a refined 2° grade. The "2°" grade refers to the boiling range of the product, which includes the normal boiling point of pyridine. Most 2° pyridine actually has a boiling-point range of <1°C and is >99.8% pure (Goe, 1982). Pyridine is also available as a 1° product specification with a maximum water content of 0.1% and an assay of 99.5% minimum.

1.3. PRODUCTION DATA

Annual production and sales figures for pyridine were last released by the U.S. Tariff Commission for 1968, when a production of 7.42 million pounds and sales of 7.55 million pounds were reported (USTC, 1970). Production figures, as reported in the public portion of the U.S. EPA TSCA Production File for 1977, are listed in Table 1-1. The current U.S. market for pyridine has been estimated to be in the thousands of tons per year (Goe, 1982). Industry capacity to produce pyridine and its derivatives is ~60

TABLE 1-1

Producers of Pyridine and Production Ranges for 1977*

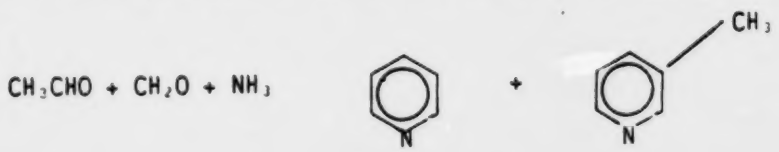
Producer and Location	Type of Producer	Production Range
Koppers Co. Follansbee, WV	manufacturer	0.1-1 million pounds
Nepera Chemical Co. Harriman, NY	manufacturer	confidential
Reilly Tar and Chemical Indianapolis, IN	manufacturer	confidential
EM Laboratories Inc. Elmsford, NY	importer/ small manufacturer	confidential
American Cyanamid Co. Bound Brook, NY	importer/ not distributed	0.1-1 million pounds
Sakai Trading Inc. New York City	importer	zero
Ruhrkohle Trading Corp. New York City	importer	confidential

*Source: U.S. EPA, 1977

million pounds annually (Table 1-2). Based upon its current uses, annual production of pyridine is ~15 million pounds.

Pyridine has been produced for the commercial market by coal-tar derived sources and by synthetic manufacture. The quantities made available from coal-tar sources is very small compared with the amounts currently made synthetically. In the coal-tar process, crude pyridine bases are produced by the coking operation of coal (Goe, 1982; Abramovitch, 1968). Every ton of coal carbonized produces 0.07-0.21 pounds of pyridine bases (57% pyridine) in the condensable and noncondensable gases generated. Isolation of the pyridine bases involves treatment with sulfuric acid, distillation and fractional distillation. Only a small percentage of the total pyridine bases generated from coking operations are refined for sale.

The synthesis method of producing pyridine involves a vapor-phase reaction of acetaldehyde, formaldehyde and ammonia to yield a mixture of pyridine and 3-methylpyridine, as shown below (Goe, 1982; Abramovitch, 1968):



Methanol is included in the feed for increased yield. The pyridine to 3-methylpyridine ratio obtained depends on the ratio of acetaldehyde to formaldehyde charged to the process.

1.4. USE DATA

An approximate use-breakdown for pyridine by percentage is as follows (Santodonato et al., 1985):

Agricultural chemicals	50%
Piperidine	18%
Pharmaceuticals	10%
Solvent applications	10%
Textile chemicals	2%
Miscellaneous uses	10%

TABLE 1-2

United States Manufacturers of Pyridine*

Manufacturer and Location	Annual Capacity (millions of Pounds)	Remarks
Crowley Tar Products Co. Kent, OH Oklahoma City, OK	NR	naturally derived from coal-tar
Nepera, Inc. Harriman, NY	25	capacity is for synthetic pyridine and pyridine derivatives
Reilly Tar and Chem. Corp. Indianapolis, IN	35	capacity is for synthetic pyridine, picolines, and other pyridine derivatives

*Source: SRI, 1985

NR = Not reported

The agriculture chemicals synthesized from pyridine include the herbicides paraquat and triclopyr and the insecticide chlorpyrifos (Goe, 1982). Piperidine is used in the synthesis of rubber accelerators and other compounds.

Substantial quantities of pyridine and its derivatives (such as amino pyridine) are used by the pharmaceutical industry. As an intermediate, pyridine is used in the synthesis of a number of antihistamines (such as chlorpheniramine maleate), steroids, sulfa-type drugs and antibacterial agents (such as cetylpyridinium chloride) (Goe, 1982; Abramovitch, 1968). It also has significant use in the pharmaceutical industry as a solvent in drug preparations; for example, it is used in the production of the sulfa drug, sulfacetamide (Doub, 1978).

In addition to solvent use in the pharmaceutical industry, pyridine is used as a solvent for synthesis in a number of industrial and laboratory applications. Industrially, pyridine is used as a solvent in the manufacture of polycarbonate resins (Fox, 1982) and in other processes in which HCl may evolve. Pyridine is commonly used in laboratory-scale reactions, such as acylation processes involving anhydrides or acid chlorides (Goe, 1982).

Pyridine is used in the synthesis of textile water repellants; Zelan-type water repellants are formed by reaction of fatty acid amides with formaldehyde, pyridine and HCl (Bathina and Reck, 1978). Marketed pyridine-derived water repellants include Zelan AP● (DuPont) and Velan PF● (Imperial Chemical); however, in recent years, the market for pyridine-derived water repellants has declined because of the toxicity of intermediates for synthesis and the superiority of fluorochemical repellants.

Pyridine has a variety of miscellaneous applications, many of which involve intermediate use. Pyridine derivatives (such as the amino pyridines) can be diazotized (Goe, 1982), and therefore are used in the production of dyestuffs. Other chemicals synthesized from pyridine include 2- and 3-bromopyridine, pyridine-N-oxide and pyridinium perbromide. In addition to solvent applications, pyridine has end-use (not involving synthesis) as an extraction of plant hormones (Kuney, 1985) and has been used as a denaturant for alcohol and antifreeze mixtures (Hawley, 1981).

1.5. SUMMARY

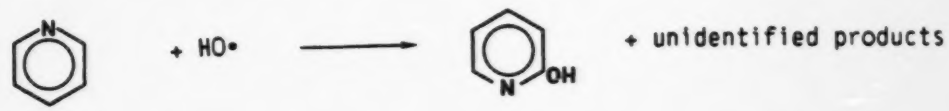
Pyridine is a colorless to yellowish hygroscopic liquid with a characteristic disagreeable odor (Jori et al., 1983). It is produced in coal tar during the coking of coal (Goe, 1982; Abramovitch, 1968); however, only a small percentage of the total pyridine generated from coking operations is refined for sale. As a commercial end-product, pyridine is predominantly produced synthetically by reacting acetaldehyde, formaldehyde and ammonia (Goe, 1982). Although the most recent production figure for pyridine is 7.42 million pounds in 1968 (USTC, 1970), the estimation of current production is ~15 million pounds annually. Pyridine has the following use-pattern (Santodonato et al., 1985): agricultural chemical synthesis, 50%; piperidine synthesis, 18%; pharmaceutical use (intermediate and solvent), 10%; solvent applications, 10%; textilie chemical synthesis, 2%; miscellaneous uses (mostly intermediate), 10%.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Pertinent data regarding the hydrolysis of pyridine could not be located in the available literature as cited in the Appendix. Pyridine does not contain functional groups that are significantly susceptible to hydrolysis; therefore, hydrolysis is not expected to be an important fate process.

2.1.2. Oxidation. Mill et al. (1979, 1980) examined the aquatic photooxidation of pyridine by $RO_2\cdot$ radicals, and found pyridine to react slowly with $RO_2\cdot$ to yield pyridine N-oxide as shown: $C_5H_5N + RO_2\cdot \rightarrow C_5H_5NO + RO\cdot$. At 50°C, the rate constant for this reaction was determined to be 0.67 M^{-1} sec^{-1}, which corresponds to a half-life of >32 years in natural waters containing an average $RO_2\cdot$ concentration of 10^{-9} M. These investigators also studied the reaction between pyridine and hydroxyl radicals and found the reaction to yield 2-, 3- and 4-hydroxypyridine and unidentified polar products as shown:



Although the reaction with HO• proceeded significantly faster than with $RO_2\cdot$, a rate constant with respect to HO• was not determined. Dorfman and Adams (1973) reported a rate constant for the reaction between pyridine and HO• at 21°C to be 1.8×10^9 M^{-1} sec^{-1}; if natural waters contain an average HO• concentration of 10^{-17} M, a half-life of 446 days can be calculated.

2.1.3. Photolysis. The absorption spectra for an aqueous solution of pyridine shows no absorption >290 nm (Jori et al., 1983); therefore, direct

photolysis in water will not occur. Mill et al. (1979, 1980) photolyzed a pure water solution of pyridine with wavelengths >300 nm and found no photolysis; however, there was a significant loss of pyridine in natural waters when irradiated with the same wavelengths in either the presence or absence of oxygen, yielding very polar products and very small amounts of hydroxypyridines and pyridine N-oxide.

2.1.4. **Microbial Degradation.** Ettinger et al. (1954) examined the degradation of pyridine in polluted water from four rivers. A concentration of 1 ppm pyridine was added to each of the river waters at 20°C; complete degradation was observed in all waters within 3-6 days. After complete degradation was noted, 1 ppm pyridine was again added to the water samples; complete degradation after recharge required only 1-3 days, indicating that the water microflora was adapting to the pyridine additions. This suggests that naturally occurring microbes are capable of adapting to and rapidly degrading pyridine.

A number of standard biodegradation tests have been conducted using pyridine and are summarized in Table 2-1. Many of these tests demonstrate that pyridine is biodegradable, particularly after an acclimation period. Gubser (1969) found pyridine 90-100% degradable after a 6- to 7-day lag period in a continuous flow activated sludge system. Malaney (1960) found pyridine to be degradable by aniline-acclimated activated sludge after a long period of acclimation.

2.1.5. **Volatilization.** Hawthorne et al. (1985) have experimentally determined the Henry's Law constant for pyridine, both as a single component dissolved in water and in mixture simulating shale oil wastewaters. The Henry's Law constants, for single component and in mixture, were found to be very similar with values determined as 1.1 and 1.2×10^{-5} atm·m³/mol at

TABLE 2-1

Results of Standard Biodegradation Tests for Pyridine

Test Method	Incubation Time (days)	Chem. Conc. (ppm)	Biodegradation Rate	Reference
Coupled Units	1	12	99% DOC removal	Gerike and Fischer, 1979
Zahn-Wellens	6	400	97% DOC removal	Gerike and Fischer, 1979
MITI	14	50	11% BODT	Gerike and Fischer, 1979
Sturm	28	10	58% CO_2 evolution	Gerike and Fischer, 1979
	42	10	97% DOC removal	
Closed Bottle	30	1	0% BODT	Gerike and Fischer, 1979
Mod. OECD	19	3-20	91% DOC removal	Gerike and Fischer, 1981
BOD	5	10	2% BODT	Young et al., 1968
	20	10	65% BODT	
MITI	14	100	"well biodegradable" O_2 consumption >30%	Sasaki, 1978
Mod. OECD	7	12.3	34% biodegradability	Ruffo et al., 1984
	14	0.9	95% biodegradability	
	21	0	100% biodegradability	
Sturm	1	10	4% biodegradability	Ruffo et al., 1984
	2		64% biodegradability	
	4	NA	81% biodegradability	
	8		94% biodegradability	
BOD	5	1.7-20	0% BODT	Heukelekian and Rand, 1955
	5	440	0% BODT	
BOD	5	NA	resistant to biodegradation	Singer et al., 1978

NA = Not available

25°C. Hine and Mookerjee (1975) have reported a unitless Henry's constant of 0.000363, which corresponds to a value of ~8.7×10^{-6} atm•m³/mol and is in reasonably good agreement with the data from Hawthorne et al. (1985). These values of Henry's constants suggest that environmental aquatic volatilization may be significant, although not rapid (Lyman et al., 1982); volatilization from shallow rivers will be more significant than from ponds or lakes.

2.1.6. **Adsorption.** The complete water solubility and relatively low log K_{ow} (0.65) of pyridine suggest that sorption of pyridine to particulate organic matter and sediment in the aquatic environment will not be significant.

The adsorption of pyridine to sodium kaolinite and montmorillonite in aqueous solution has been studied experimentally (Baker and Luh, 1971; Luh and Baker, 1971). It was found that sorption does not occur at pHs >7; however, significant sorption did occur in acidic solution. The sorption in acidic solution was attributed to cation exchange and was found to increase in the region of pyridinium ion formation. With a pKa of 5.22, pyridine exists predominantly in the pyridinium ion form in acidic solution, but not in basic solution.

2.1.7. **Bioaccumulation.** The complete water solubility and relatively low log K_{ow} (0.65) of pyridine indicate that bioaccumulation in aquatic organisms is not expected to be important.

2.2. AIR

2.2.1. **Reaction with Hydroxyl Radical.** The rate constant for the reaction between pyridine and OH• radical in gas-phase at 25°C has been experimentally determined to be $<1 \times 10^{-12}$ cm³/molecule-sec (Atkinson, 1985). Assuming an average atmospheric OH radical concentration of 10^6

molecules/cm³, the half-life for this reaction is calculated to be >8 days. This will be the dominant chemical removal mechanism for pyridine in air.

2.2.2. **Reaction with Atomic Oxygen.** The rate constant for the reaction between pyridine and O(³P) has been reported to be 1.66×10^{-13} cm³/molecule-sec at 25°C (Herron and Huie, 1973); assuming an average atmospheric O(³P) concentration of 5×10^{4} molecules/cm³, a half-life in excess of 2.5 years is calculated indicating little environmental importance.

2.2.3. **Photolysis.** Pyridine does not absorb solar radiation >300 nm (Jori et al., 1983; Sadtler, 1961); therefore, direct photolysis of pyridine will not occur in the troposphere.

2.2.4. **Physical Removal Mechanisms.** The complete water solubility of pyridine suggests that removal from the atmosphere by rainfall as washout or by dissolution into clouds with subsequent rainfall is possible. The overall relative significance of rainfall as a removal mechanism is not clear.

2.3. SOIL

2.3.1. **Microbial Degradation.** Naik et al. (1972) examined the degradation of 1 mM solution of pyridine in an aqueous suspension of 0.5% fertile garden soils, yeast extract, peptone, glucose and mineral salts. Tightly closed incubation tubes were used to simulate anaerobic conditions, while loosely capped tubes simulated aerobic conditions. Complete pyridine decomposition occurred in 66-170 days under aerobic conditions and in 32-66 days under anaerobic conditions.

The biodegradation of pyridine has been tested in various pure culture studies in which the microorganisms were isolated from soil. Moore (1949) found that various strains of Proactinomyces were able to use pyridine as a sole source of carbon, nitrogen and energy; however, strains of Pseudomonas and Actinomyces isolated from the same soil were unable to degrade pyridine.

Korosteleva et al. (1981) found that Nocardia sp. strain KM-2, which was isolated from soil near a coal-tar plant, was able to use pyridine as a sole carbon and nitrogen source. Watson and Cain (1975) determined that species of Bacillus and Nocardia were able to grow rapidly on pyridine as sole carbon, nitrogen and energy source. Shukla (1973) found Corynebacterium sp. and Brevibacterium sp. capable of degrading pyridine. Various methylotropic bacteria are also able to degrade pyridine (Haber et al., 1983).

2.3.2. **Adsorption.** Experimental data predicting the adsorption of pyridine in soils were not found. The complete water solubility and low log K_{ow} (0.65) suggest that pyridine will be very mobile in soil and easily leached. Baker and Luh (1971) found that pyridine was not adsorbed by clay particles in aqueous solution at pHs >7, although the Pyridium ion was adsorbed in acidic conditions. Prediction of soil adsorption by the molecular topology and quantitative structure-relationship analysis method of Sabljic (1984) yields a K_{oc} of 125, which is indicative of significant soil mobility.

2.3.3. **Volatilization.** The relatively high vapor pressure of pyridine (20 mm Hg at 24.8°C) indicates rapid evaporation from dry surfaces. In moist soil conditions, however, leaching will likely cause the rate of evaporation to be significantly reduced.

2.4. SUMMARY

Several environmental fate processes may contribute to the removal of pyridine from the aquatic environment, with microbial degradation, perhaps, being the most important overall. Ettinger et al. (1954) have shown that four different polluted river waters were able to completely biodegrade pyridine in 3-6 days with only 1-3 days required for degradation upon pyridine readdition to the waters, indicating rapid adaption of the microbes.

A number of standard biodegradation tests have demonstrated the biodegradability of pyridine, particularly after acclimation (see Table 2-1). Experimentally measured Henry's Law constants (Hawthorne et al., 1985; Hine and Mookerjee, 1975) of ~10^{-5} atm•m³/mol suggest significant, but not rapid, volatilization from environmental waters (Lyman et al., 1982), with volatilization from shallow rivers being most significant. Mill et al. (1979, 1980) found that irradiation of natural waters containing pyridine with wavelengths >300 nm resulted in significant loss of pyridine, even though irradiation of pure water solutions of pyridine produced no degradation. Aquatic hydrolysis, oxidation by RO_2• or HO• radicals, adsorption, and bioaccumulation in organisms are not expected to be environmentally important.

Once exposed to the ambient atmosphere, reaction with hydroxyl radicals is expected to be the dominant chemical removal mechanism for pyridine. Based on an experimentally determined rate constant for hydroxyl radical reaction of <$1x10^{-12}$ cm³/molecule-sec (Atkinson, 1985), a half-life >8 days can be calculated for an average atmosphere. Removal of pyridine from the atmosphere by rainfall may be possible, since it is completely water soluble. The biodegradation of pyridine by soil microorganisms has been demonstrated (Naik et al., 1972; Moore, 1949; Korosteleva et al., 1981; Watson and Cain, 1975; Shukla, 1973; Haber et al., 1983). Although experimental soil adsorption data are not available, pyridine is expected to be very mobile in soil and easily leached, based on its water solubility, log K_{ow} (0.65) and chemical structure. Pyridine is expected to evaporate quite rapidly from dry surfaces based on its vapor pressure (20 mm Hg at 24.8°C).

3. EXPOSURE

3.1. WATER

Stuermer et al. (1982) detected pyridine in three groundwater samples collected from three wells near two underground coal gasification sites 15 months after the gasification had ended; the pyridine concentration in the three samples measured 0.82, 53 and 49 ppb.

Pyridine has been detected in wastewaters resulting from shale oil operations at concentrations ranging from 5-152 ppm (Pellizzari et al., 1979; Dobson et al., 1985; Hawthorne and Sievers, 1984). Concentrations of 117 ppm have also been detected in wastewaters resulting from coal conversion processes (Singer et al., 1978). Waggot (1981) found trace levels of pyridine in the River Lee in England, near an effluent discharge point from a sewage-treatment works. Shackelford and Keith (1976) have reported the detection of pyridine in various chemical and coking works effluents.

The major source of pyridine exposure to ambient waters is probably wastewater discharges resulting from various industrial and energy-related processes.

3.2. FOOD

Monitoring data regarding pyridine detection in food is very limited. Pyridine has been detected in the volatile flavor components of fried chicken (Tang et al., 1983) and roasted barley (Wang et al., 1969). It has also been detected in waste gases from coffee roasting (Tijmensen, 1978).

3.3. INHALATION

Pyridine has been detected in atmospheric effluents resulting from coal coking operations (Anonymous, 1979; Gracheva et al., 1983; Gradel, 1978), in the waste gases of a coffee roasting factory (Tijmensen, 1978), and in flue gas emissions from cold-box molding foundries (Schandl et al., 1984). The ambient air downwind of a coal gasification plant in Yugoslavia was found to

contain pyridine (Lee et al., 1982). Hawthorne and Sievers (1984) determined that pyridine was emitted to the air by volatilization from shale oil wastewaters. Zeman and Koch (1983) found pyridine in the air in sewage plants. Pyridine has also been detected in residential homes in the Chicago area (Jarke et al., 1981).

Pyridine has been identified as a component of tobacco (Schmeltz et al., 1979), cigar (Osman and Barson, 1964) and marijuana (Novotny et al., 1982) smoke.

3.4. DERMAL

Pertinent dermal monitoring data could not be located in the available literature as cited in the Appendix. Risk of dermal exposure may be greatest to workers using pyridine as a solvent.

3.5. SUMMARY

Pyridine has been detected in wastewaters associated with shale oil processing (Pellizzari et al., 1979; Dobson et al., 1985; Hawthorne and Sievers, 1984), coal conversion processes (Singer et al., 1978), and chemical and coke manufacturing (Shackelford and Keith, 1976). These industrial and energy-related processes are probably the major source of pyridine exposure to ambient waters. Food detections of pyridine include the volatile flavor components of fried chicken (Tang et al., 1983) and roasted barley (Wang et al., 1969) and waste gases from coffee roasting (Tijmensen, 1978). Sources of industrial pyridine emissions to the atmosphere include coal coking operations (Anonymous, 1979; Gracheva et al., 1983; Graedel, 1978), coffee roasting (Tijmensen, 1978), coal gasification (Lee et al., 1982), cold-box molding foundry emissions (Schandl et al., 1984), and volatilization from shale oil wastewaters (Hawthorne and Sievers, 1984). Pyridine has been identified as a component of tobacco (Schmeltz et al., 1979), cigar (Osman and Barson, 1964) and marijuana (Novotny et al., 1982) smoke.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pyridine is absorbed through the respiratory and gastrointestinal tracts (Gleason et al., 1976). Data regarding the dermal absorption of pyridine could not be located in the available literature as cited in the Appendix.

D'Souza et al. (1980) administered 3.4 mg of [2.6-^{14}C]-pyridine hydrochloride in orange juice to each of two human male subjects, who excreted 65 and 68% of the administered radioactivity in the urine collected over 24 hours. These results indicate that pyridine was rapidly and extensively absorbed from the gastrointestinal tract of humans.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of pyridine could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Pyridine may be methylated at the N-position (Reinhardt and Brittelli, 1981) and excreted as N-methyl pyridinium hydroxide, its chief metabolite (Browning, 1965). Some pyridine is excreted unchanged. N-methylation of pyridine has been shown to occur in the rat, mouse, gerbil, hamster, guinea pig, cat, rabbits and man (D'Souza et al., 1980). Guinea pigs, hamsters and gerbils excreted 20-33% of the intraperitoneal dose (7.7 mg/kg) of ^{14}C-pyridine as N-methyl-^{14}C-pyridinium in the urine collected over 24 hours. Cats excreted 40% of the dose as the metabolite; the urine was collected for 48 hours. Excretion of N-methylpyridinium accounted for 5-12% of the oral dose in humans, 5% of the intraperitoneal dose in the rat and 12% in the mouse in 24 hours. In rabbits, urine collected for 72 hours contained 15-26% of the dose as N-methylpyridinium. In the rat and guinea pig, the proportion of pyridine methylated was independent of the route of administration (oral or intraperitoneal) (D'Souza et al., 1980).

4.4. EXCRETION

Pyridine may be excreted primarily unchanged or methylated at the N-position (Reinhardt and Brittelli, 1981) and excreted as N-methyl pyridinium hydroxide (Browning, 1965). In addition to N-methylpyridinium, the following urinary metabolites have been identified in the urine of Golden Syrian hamsters following an intraperitoneal dose of ^{14}C-pyridine (7 mg/kg bw, ~10 μCi): pyridine N-oxide, 3-hyrdoxypyridine, 4-pyridone, 2-pyridone (Shaker et al., 1982). The results were reported to be typical of several other unspecified animal species.

The excretion of N-methylpyridinium was dose dependent in rats and guinea pigs. Following intraperitoneal doses of 1, 7 and 500 mg/kg, urinary excretion of N-methylpyridinium within 24 hours accounted for 9.8, 5.0 and 0.8%, respectively, of the administered dose in guinea pigs. Urinary excretion of ^{14}C in the rat accounted for 70, 48 and 5.8% of the administered doses of 1, 7 and 500 mg/kg, respectively, within 24 hours. In the guinea pig, urinary excretion of ^{14}C accounted for 79, 66 and 11%, respectively, of the administered doses (D'Souza et al., 1980). In both species the metabolic reaction was saturable but the guinea pig appears to have a greater capacity for methylation.

4.5. SUMMARY

Absorption of pyridine occurs through the respiratory and gastrointestinal tracts (Gleason et al. 1976). Gastrointestinal absorption of ^{14}C-pyridine by human volunteers was rapid and extensive (D'Souza et al., 1980). Data regarding the distribution of pyridine could not be located in the available literature as cited in the Appendix. In vivo methylation of pyridine occurs at the N-position and the chief excretory metabolite is N-methyl pyridinium hydroxide (Reinhardt and Brittelli, 1981; Browning,

1965; D'Souza et al., 1980). Methylation of pyridine has been shown to occur in eight species (rat, mouse, gerbil, hamster, guinea pig, cat, rabbit and man) (D'Souza et al., 1980). Methylation was independent of route (oral or intraperitoneal), but the fraction of the dose methylated decreased with increasing doses in rats and guinea pigs. Other urinary metabolites have been identified from the urine of Golden Syrian hamsters (pyridine N-oxide, 3-hydroxypyridine, 4-pyridone and 2-pyridone) (Shaker et al., 1982).

5. EFFECTS

5.1. CARCINOGENICITY

Derse (1969) injected neonatal mice (Random-bred Texas-Yale) subcutaneously with either 0.133 or 1.33 mg of pyridine and observed them for 15 months. No significant differences in neoplastic lesions were seen between test and control mice. Subcutaneous injection of 0, 3.0, 10.0, 30.0 or 100.0 mg/kg of pyridine in groups of 20-80 F-344 male and female rats, 2 times/week for 52 weeks and observed for an additional 6 months did not result in an increased incidence of tumors compared with controls, although sarcomas developed at the injection site in 1-2% of both treated and control rats (Mason et al., 1969, 1971).

Homburger (1968) injected 100 male C57Bl/6 mice (7 weeks old) subcutaneously with 6 mg pyridine/mouse. Five weeks later, tissue from the injection sites was injected into 25 mice serving as secondary hosts. No evidence of a carcinogenic effect was observed. In a pulmonary adenoma assay, groups of 50 CFl and 50 A/Jax female mice received a single intravenous dose of 6.0 mg pyridine/mouse (Homburger, 1968). Another group of 20 CFl female mice received seven injections at monthly intervals of 6.0 mg/mouse/injection. The mice were killed at 28 weeks after the single or the last repeated injection. No significant increased incidence of pulmonary adenomas was observed compared with controls. In another experiment, Homburger (1968) injected 50 male C57Bl/6 mice subcutaneously with dibenzpyrene. Pyridine at 6 mg/mouse/injection was injected 24 hours, 7 and 14 days later and the mice were killed 29-31 weeks after the start of the experiment. The results of this co-carcinogenicity study were inconclusive.

Pyridine has been tested in the National Toxicology Program (NTP) carcinogenesis testing program. The chemical was administered by gavage to rats and mice. but the report is not yet available (NTP, 1985).

5.2. MUTAGENICITY

Results of mutagenicity testing are summarized in Table 5-1. Pyridine was found to be nonmutagenic when tested both with and without metabolic activation in the Ames assay for mutagenicity towards four histidine-requiring mutants of Salmonella typhimurium (TA98, TA100, TA1535 and TA1537) (Florin et al., 1980). Similar results for the Ames assay were reported by Burrell et al. (1983) and Riebe et al. (1982). Pyridine was found to be not mutagenic in reverse mutation and rec assays with Escherichia coli (Riebe et al., 1982; Pai et al., 1978). In cytogenetic assays with Chinese hamster cells, pyridine increased the frequency of SCE, but not chromosome aberrations (Abe and Sasaki, 1977; Ishidate and Odashima, 1977).

5.3. TERATOGENICITY

Landauer and Salam (1974) evaluated the effect of pyridine on chick development. A treatment of 20 mg/egg injected at 96 hours of incubation resulted in muscular hypoplasia of the legs and occasional abnormalities of the facial skeleton and neck vertebrae.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding reproductive effects of pyridine could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic oral toxicity of pyridine could not be located in the available literature as cited in the Appendix. Subchronic studies have been done using pyridine, but many of these are short (i.e., <90 days); the findings, however, consistently support a hepatotoxic effect of pyridine. Groups of 35 male and 35 female rats (strain not specified) fed diets containing 0.6% (6000 ppm) pyridine for 28 days, regardless of "protective" supplements such as choline, cystine and methionine, exhibited

TABLE 5-1

Mutagenicity Testing of Pyridine

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537	≥97%	spot test	30 µmol/plate	±S-9	=	NC	Florin et al., 1980
Reverse mutation	S. typhimurium TA100	NR	NR	NR	±S-9	=	NC	Burrell et al., 1983
Reverse mutation	S. typhimurium TA98, TA100, TA1537	NR	plate incorporation	32, 16, 8, 1.6 and 0.32 mM	±S-9	=	NC	Riebe et al., 1982
Reverse mutation	E. coli WP2 uvrA	NR	spot test	5-10 mg	none	-	NC	Pai et al., 1978
Rec assay	Escherichia coli 343/113 pol A+; KMBL 1787 pol A-	NR	spot test	10 µg	none	-	NC	Riebe et al., 1982
Sex-linked recessive lethals	Drosophila melanogaster	technical grade	feed and injection	600 and 700 ppm feed; 7000 ppm injection	NA	-	Questionable results by feeding; not mutagenic by injection	Valencia et al., 1985
SCE	Chinese hamster cells	NR	culture	$1x10^{-8}$ to $5x10^{-8}$ M	none	+	Increased frequency of SCEs, but no dose response	Abe and Sasaki, 1977
Chromosome aberrations	Chinese hamster cells	NR	culture	$1x10^{-8}$ M $2x10^{-8}$ M $5x10^{-8}$ M	none	-	NC	Abe and Sasaki, 1977
Chromosome aberrations	Chinese hamster cells	NR	culture	4 mg/L	none	-	NC	Ishidate and Odashima, 1977

NR = Not reported; NA = not applicable; NC = no comment

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increased mortality, as well as hepatomegaly, over controls (Coulson and Brazda, 1948). There was no effect on food consumption or body weight gain. In addition to marked liver enlargement, histological examination of pyridine-treated rat livers revealed small, irregular vacuoles and severe necrosis. The increased mortality of the rats was thought to be due to liver failure. Renal damage was also observed in treated animals, but was less severe than the hepatic damage. Only the livers and kidneys were examined histologically.

Male Sprague-Dawley or Sherman rats ingesting 3400-10,000 ppm of pyridine citrate (1000-3000 ppm pyridine) or 1000-12,000 ppm pyridine for 28 days to 4 months developed enlarged necrotic and cirrhotic livers and degenerating renal tubular epithelium (Baxter, 1946, 1948, 1949; Baxter and Mason, 1947; Hove, 1953). Most of the rats died within 1-4 weeks. Hepatotoxicity and nephrotoxicity were also reported in the rats that died within 1-2 weeks of pyridine treatment. Dietary supplements of methionine, cystine and α-tocopherol increased the survival rate of pyridine-treated rats, but had no effect on decreasing the severity of hepatic lesions (Baxter, 1948; Baxter and Mason, 1947; Coulson and Brazda, 1948; Hove, 1953).

Results of the preliminary testing for the chronic gavage study being conducted by NTP (1985) are available; however, these data have not been peer reviewed nor verified by the NTP. In the preliminary study groups of 10 male and 10 female B67C3F1 mice were treated with pyridine by gavage at 0, 25, 50, 100, 200 or 400 mg/kg/day, 5 days/week for 13 weeks (GSRI, 1979). Deaths occurred in 1/10 and 6/10 male mice at the 200 and 400 mg/kg/day dose levels, respectively, beginning at week 8 of treatment. No deaths occurred in female mice. A dose-related decreased body weight gain was reported in male mice at $\geq$25 mg/kg/day ranging from 6% at the lowest dose to 40% at the highest (400 mg/kg/day) level, compared with controls. Female mice showed

little difference in weight gain as compared with controls, with all the treated groups weighing more than the controls.

All mice that died or were killed at the end of the study were necropsied. Comprehensive histological examination was performed on the control and high-dose groups. Histological examination of the 100 and 200 mg/kg/day groups was limited to the liver and gross lesions. No histological examinations were performed on the 25 and 50 mg/kg/day dose groups. GSRI (1979) reported that histopathological liver lesions consisting of fatty metamorphosis, hepatocytomegaly and multifocal necrosis occurred in all high-dose males and females, and 2/10 females at the 200 mg/kg/day dose levels. No liver lesions were found in the 200 mg/kg/day males nor in the 100 mg/kg/day mice or controls. In a quality assessment of this study conducted by Tracor Gitco, Kovatch (1979) found liver inflammation in 1/01 males and 2/10 females at the 100 mg/kg/day level and 5/10 males and 4/10 females at the 200 mg/kg/day level.

In this preliminary study GSRI (1979) also treated groups of 10 male and 10 female F344 rats with pyridine by gavage at 0, 12.5, 25, 50, 100 and 200 mg/kg/day, 5 days/week for 13 weeks. Deaths occurred in 1/10 males in the 100 and 200 mg/kg/day dose levels and 2/10 females at 200 mg/kg/day. All dosed groups of females and reduced body weight gain, while males had decreased body weight at levels $\geq$50 mg/kg/day compared with controls. Necropsies and histological examinations were performed as described previously for mice. Liver lesions, consisting of cirrhosis of multiple focal necrosis, hepatocytomegaly, bile duct hyperplasia or fatty metamorphosis, occurred in 8/10 males and 10/10 females at 200 mg/kg/day, and 6/10 males and 8/10 females at 100 mg/kg/day. Lesions in the heart, indicative of focal interstitial myocarditis, were found in 4/10 males and 3/10 females at 200 mg/kg/day. The heart tissue of the other groups was not examined.

In their assessment of this study, Kovatch (1979) reported the 2/10 female rats receiving 50 mg/kg/day pyridine had liver lesions described as chronic inflammation, multifocal fibrosis and bile stasis. Kovatch (1979) also reported that 100% of the rats receiving 100 and 200 mg/kg/day pyridine had liver lesions and that heart lesions occurred in 4/10 and 5/10 high-dose males and females, respectively, and that high-dose rats but not the controls had kidney lesions (5/10 males, 6/10 females). The kidneys of the other treatment groups were not examined microscopically.

Ingestion of pyridine has been reported in humans. Gleason et al. (1976) reported that small oral doses of 2-3 mℓ (1.96-2.94 g) pyridine in man resulted in mild anorexia, nausea, fatigue and depression. Doses of 0.31-2.46 mℓ of pyridine/day (0.30-2.42 g/day) were given to 5 patients for periods up to 2 months for the treatment of epilepsy (Pollock et al., 1943). Minor complaints such as anorexia, nausea, headache, occasional vomiting, weakness, faintness and depression were observed in four of the patients receiving 0.30-1.51 g pyridine/day. Otherwise, there was no evidence of organ damage. When the treatment was continued at a higher dosage (1.85 and 2.46 mℓ, or 1.82 and 2.42 g pyridine/day) in two patients, the results were unfavorable. Severe toxicity, as evidenced by hepatic involvement and renal insufficiency, developed in one patient after 11 days of treatment. Following a blood transfusion, the patient recovered to his pre-pyridine condition. In the second case, there was rapid development of jaundice and anuria with evidence of progressive parenchymal destruction of the liver. Death occurred 8 days after the onset of the acute symptoms and was attributed to hepatorenal failure (Pollock et al., 1943).

In a study summarized in the Encyclopedia of Occupational Safety and Health (1983), an unspecified number of rats were exposed to 10 or 50 ppm (32.35 or 161.75 mg/m^3) pyridine vapor for 7 hours/day, 5 days/week for 6 months. An increase in relative liver weight compared with controls was observed in the treated rats, but there was no effect on growth rate or mortality. The source and additional details were not provided in the summary.

The effects of pyridine inhalation on humans have been reported by several authors (Pollock et al., 1943; Browning, 1965; Teisinger, 1948) and include the following: headache, temporary vertigo, nausea, occasional vomiting, flushing of face, quickening of pulse and respiration, sleeplessness and temporary giddiness. (Details of exposure are imprecise in many of these studies.) Pyridine was used in the 1800's for the treatment of asthma (Pollock et al., 1943). A 10% solution by atomizer application was apparently administered "safely" to asthmatic patients (Fairhall, 1949).

Teisinger (1948) reported an occupational exposure of 6-12 ppm (19-39 mg/m^3), which resulted in the above symptoms in seven employees; however, vapors from other chemicals were also reported in the air. Reinhardt and Brittelli (1981) reported that human exposure to 125 ppm (404 mg/m^3) of pyridine for 4 hours/day for 1-2 weeks produced the same symptoms, in addition to lower back and abdominal discomfort and urinary frequency. There was no evidence of liver or kidney damage.

5.6. OTHER RELEVANT INFORMATION

Acute toxicity data for pyridine are presented in Table 5-2.

5.7. SUMMARY

Chronic or subchronic studies regarding the oral or inhalation carcinogenicity of pyridine could not be located in the available literature as

TABLE 5-2

Acute Toxicity of Pyridine[a]

Species	Route	Dose	Response
Rat	oral	0.8-1.6 g/kg	Approximate LD_{50}[b]
	oral	1.58 g/kg	LD_{50}
	oral	0.1% in diet	Deaths, liver and kidney injury
Rat	inhalation	9000 ppm, 1 hour	LD_{50}
	inhalation	23,000 ppm, 1.5 hour	6/6 died
	inhalation	3600 ppm, 6 hours	2/3 died
	inhalation	4000 ppm, 4 hours	5/6 died
	inhalation	saturated vapor 30 minutes	Maximum for no deaths
	subcutaneous	866 mg/kg	LD_{50}
	subcutaneous	1000 mg/kg	LD_{50}
Mouse	oral	0.8-1.6 g/kg	Approximate LD_{50}[b]
	intraperitoneal	0.8-1.6 g/kg	Approximate LD_{50}[b]
	intraperitoneal	12,000 mg/kg	LD_{Lo}
Guinea pig	intraperitoneal	0.87 g/kg	Lethal dose
	skin	1-2 mL/kg	Approximate LD_{50}
	eye	1 drop, undiluted	Corneal damage
	oral	4000 mg/kg	LD_{Lo}
Rabbit	eye	40% solution	Corneal necrosis
	skin absorption	1121 mg/kg	LD_{50}
	skin irritation	undiluted	Strong, capillary injection

[a]Source: Reinhardt and Brittelli, 1981

[b]All died at the 1.6 g/kg dose and all survived at the 0.8 g/kg dose.

cited in the Appendix. The technical report of a chronic gavage study in rats and mice is not yet available (NTP, 1985). No evidence of carcinogenicity was found in rats and mice administered pyridine in subcutaneous and intravenous studies (Mason, 1969; Mason et al., 1971; Homburger, 1968; Derse, 1969).

Pyridine was found to be nonmutagenic when tested for reverse mutation with and without metabolic activation in four strains of Salmonella typhimurium and one strain of Escherichia coli (Florin et al., 1980; Burrell et al., 1983; Riebe et al., 1982; Pai et al., 1978). Pyridine was also negative in a rec assay in E. coli (Reibe et al., 1982). Pyridine increased the frequency of SCE, but not chromosome aberrations, in Chinese hamster cells (Abe and Sasaki, 1977; Ishidate and Odashima, 1977).

One limited study was located on the effect of pyridine on reproduction and teratology. Landauer and Salam (1974) treated chicken eggs with 20 mg pyridine/egg at 96 hours of incubation and found muscular hyperplasia of the legs and occasional abnormalities of the facial skeleton and neck vertebrae in the chicks.

Chronic oral toxicity studies could not be located in the available literature as cited in the Appendix. Several short-term studies (Baxter, 1946, 1948; Baxter and Mason, 1947; Hove, 1953; Coulson and Brazda, 1948) have evaluated the toxicity of dietary pyridine to young rats; however, these studies were conducted for 1-4 months and many of the rats died during the first few weeks of treatment. The results consistently support a hepatotoxic effect of pyridine. Dietary concentrations of pyridine in these studies ranged from ~1000-10,000 ppm. Most rats died in the first 2-3 weeks of treatment; hepatomegaly, liver necrosis and cirrhosis, and degeneration of the renal tubular epithelium were consistently reported (Baxter, 1946, 1948; Baxter and Mason, 1947; Coulson and Brazda, 1948; Hove, 1953).

Mice treated with pyridine by gavage, 5 days/week for 13 weeks had dose-related decreased body weight gain (males) at ≥25 mg/kg and dose-related increased incidence of liver lesions at levels ≥100 mg/kg/day. Livers of mice treated at levels ≤100 mg/kg/day were not examined microscopically. Deaths occurred in 1/10 and 6/10 males treated with pyridine at 200 and 400 mg/kg/day, respectively. Rats similarly treated had reduced body weight gain at ≥12.5 mg/kg/day (lowest dose tested) and dose-related increased incidence of liver lesions at levels ≥50 mg/kg/day. In adidtion, high-dose rats had increased incidences of interstitial myocarditis and glomerulo-nephritis compared with controls. Death occurred in 1/10 males at 100 and 200 mg/kg/day levels and in 2/10 females at the 200 mg/kg/day level.

Inhalation exposure of rats to 10 or 50 ppm (32 or 162 mg/m^3), 7 hours/day, 5 days/week for 6 months resulted in increased relative liver weight, but had no effect on growth or mortality (Encyclopedia of Occupational Safety and Health, 1983).

Toxic effects such as headaches, nervousness, sleeplessness, nausea and vomiting have been reported in humans from occupational exposure to 6-12 ppm pyridine (19-39 mg/m^3) (Teisinger, 1948). Pollock et al. (1943) reported similar symptoms in five epileptic humans given pyridine orally at 0.30-1.51 g/day. When the dosage was increased to 1.82 g/day, renal insufficiency and evidence of altered hepatic function occurred. At a dose of 2.42 g pyridine/day, death as a result of hepatorenal failure was reported. Despite the lack of adequate long-term studies, pyridine does appear to be hepatotoxic.

6. AQUATIC TOXICITY

6.1. ACUTE

The available data regarding acute toxicity of pyridine to fish is summarized in Table 6-1. Among the species tested, carp, Cyprinus carpio, appear to be the most sensitive, with a 96-hour LC_{50} of 26 mg/ℓ (Rao et al., 1975). The most resistant species are the guppy, Poecilia reticulata, medaka, Oryzias latipes, and mosquitofish, Gambusia affinis, all with 48-hour LC_{50} values >1000 mg/ℓ.

There is limited information about toxic effects of pyridine on tadpoles (Table 6-2). These data indicate LC_{50} values similar to those of the resistant fish species (~1000 mg/ℓ). Pyridine affected development of tadpoles at lower concentrations, however, with an increased incidence of abnormal tadpoles over control groups at concentrations as low as 10 mg/ℓ (Dumont et al., 1979).

Table 6-3 contains the available information concerning toxicity of pyridine to various invertebrate species. There is a wide range in sensitivity among protozoa. The flagellates, Entosiphon subcatum and Chilomonas paramecium, were the most sensitive of the species tested, having toxic thresholds for inhibition of cell multiplication of 3.5 and 3.9 mg/ℓ, respectively (Bringmann and Kuehn, 1980; Slooff et al., 1983), but these results were not confirmed in other studies (Bringmann and Kuehn, 1981). LC_{50} values among benthic insects ranged from 30 mg/ℓ for Corixa punctata to 410 mg/ℓ for Ischnura elegans (Slooff, 1983). Planktonic cludocerans were less sensitive than the insects, with LC_{50} values ranging from 240 mg/ℓ for Daphnia magna (Bringmann and Kuehn, 1977) to 2470 mg/ℓ for Daphnia cucullata (Canton and Adema, 1978).

TABLE 6-1

Summary of Data Concerning Acute Toxicity of Pyridine to Fish

Species	Duration (hours)	Concentration (mg/l)	Response	Reference
Bluegill, Lepomis macrochirus	24	5	no observed effect	Applegate et al., 1957
Rainbow trout, Salmo gairdneri	24	5	no observed effect	Applegate et al., 1957
Sea lamprey, Petromyzon marinus	24	5	no observed effect	Applegate et al., 1957
Carp, Cyprinus carpio	24	47.5	LC_{50}	Rao et al., 1975
Carp, Cyprinus carpio	48	35.0	LC_{50}	Rao et al., 1975
Carp, Cyprinus carpio	96	26.0	LC_{50}	Rao et al., 1975
Fathead minnow, Pimephales promelas	48	82	no observed mortality	Slooff et al., 1983
Fathead minnow, Pimephales promelas	48	115	LC_{50}	Slooff et al., 1983
Cyprinid, Alburnus sp.	NR	100	toxicity threshold	McKee and Wolf, 1963
Bleak, Alburnus alburnus	NR	160	toxicity threshold	McKee and Wolf, 1963
Bream, Albramis bramia	NR	180	toxicity threshold	McKee and Wolf, 1963
Carp, Cyprinus carpio	NR	200	toxicity threshold	McKee and Wolf, 1963
"Perch"	NR	200	no adverse effect	McKee and Wolf, 1963
Golden orfe, Leuciscus idus	48	137-147	LC_0	Juhnke and Ludemann, 1978
Golden orfe, Leuciscus idus	48	225-240	LC_{50}	Juhnke and Ludemann, 1978
Golden orfe, Leuciscus idus	48	284-294	LC_{100}	Juhnke and Ludemann, 1978
Golden orfe, Leuciscus idus	48	196	LC_{50}	Slooff et al., 1983
Medaka, Oryzias latipes	48	330	LC_{50}	Tonogai et al., 1982
Medaka, Oryzias latipes	24	400	LC_{50}	Tonogai et al., 1982
Rainbow trout, Salmo gairdneri	24	540	24-hour LC_{50}	Jori et al., 1983
Rainbow trout, Salmo gairdneri	48	460	no observed mortality	Slooff et al., 1983
Rainbow trout, Salmo gairdneri	48	560	LC_{50}	Slooff et al., 1983
Guppy, Poecilia reticulata	48	1100	no observed mortality	Slooff et al., 1983
Guppy, Poecilia reticulata	48	1390	LC_{50}	Slooff et al., 1983
Medaka, Oryzias latipes	48	1420	no observed mortality	Slooff et al., 1983
Medaka, Oryzias latipes	48	1560	LC_{50}	Slooff et al., 1983
Mosquitofish, Gambusia affinis	24;48	1350	LC_{50}	Wallen et al., 1957
Mosquitofish, Gambusia affinis	96	1300	LC_{50}	Wallen et al., 1957

NR = Not reported

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TABLE 6-2

Summary of Data Concerning Acute Toxicity of Pyridine to Larval Amphibians

Species	Duration (hours)	Concentration (mg/ℓ)	Response	Reference
Ambystoma mexicanum	48	950	LC_{50}	Slooff and Baerselman, 1980
Ambystoma mexicanum	48	700	no observed mortality	Slooff et al., 1983
Xenopus laevis	96	0	100% survived, 0% abnormal	Dumont et al., 1979
Xenopus laevis	96	10	98% survived, 6% abnormal	Dumont et al., 1979
Xenopus laevis	96	50	96% survived, 33% abnormal	Dumont et al., 1979
Xenopus laevis	120	850	teratogenicity EC_{50}	Davis et al., 1981
Xenopus laevis	120	1000-1050	LC_{50}	Davis et al., 1981
Xenopus laevis	48	1150	no observed mortality	Slooff et al., 1983
Xenopus laevis	48	1400	LC_{50}	Slooff et al., 1983

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TABLE 6-3

Summary of Data Concerning Acute Toxicity of Pyridine to Invertebrates

Species	Duration (hours)	Concentration (mg/ℓ)	Response	Reference
		PROTOZOA		
Tetrahymena pyriformis	NR	1194	IGC_{50}	Schultz and Allison, 1979
Tetrahymena pyriformis	NR	2500	100% inhibition of population growth	Schultz and Allison, 1979
Entosiphon sulcatum	NR	13	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Entosiphon sulcatum	NR	11	same as above	Slooff et al., 1983
Entosiphon sulcatum	NR	3.5	same as above	Bringmann and Kuehn, 1980
Uronema parduczi	NR	180	same as above	Slooff et al., 1983
Uronema parduczi	NR	97	same as above	Bringmann and Kuehn, 1981
Chilomonas paramecium	NR	3.9	same as above	Slooff et al., 1983
Chilomonas paramecium	NR	>400	same as above	Bringmann and Kuehn, 1981
Microregma sp.	NR	200	toxicity threshold	McKee and Wolf, 1963
		INSECTS		
Heteroptera, Corixa punctata	48	30	LC_{50}	Slooff, 1983
Odonata, Ischnura elegans	48	410	LC_{50}	Slooff, 1983
Plecoptera, Nemoura cinera	48	254	LC_{50}	Slooff, 1983
Ephemeroptera, Cloeon dipterum	48	165	LC_{50}	Slooff, 1983
Diptera, Chironomus gr. thummi	48	229	LC_{50}	Slooff, 1983
Diptera, Aedes aegypti	48	130	LC_{50}	Slooff et al., 1983
Diptera, Aedes aegypti	48	55	no observed mortality	Slooff et al., 1983
Diptera, Culex pipiens	48	66	LC_{50}	Slooff et al., 1983
Diptera, Culex pipiens	48	38	no observed mortality	Slooff et al., 1983

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TABLE 6-3 (cont.)

Species	Duration (hours)	Concentration (mg/ℓ)	Response	Reference
		CRUSTACEANS		
Cladoceran, Daphnia magna	24	2114	LC_{50}	Dowden and Bennett, 1965
Cladoceran, Daphnia magna	48	944	LC_{50}	Dowden and Bennett, 1965
Cladoceran, Daphnia magna	48	70	LC_{0}	Bringmann and Kuehn, 1977
Cladoceran, Daphnia magna	48	240	LC_{50}	Bringmann and Kuehn, 1977
Cladoceran, Daphnia magna	48	910	LC_{100}	Bringmann and Kuehn, 1977
Cladoceran, Daphnia magna	24	266	EC_{0}, immobilization	Bringmann and Kuehn, 1982
Cladoceran, Daphnia magna	24	520	EC_{50}, immobilization	Bringmann and Kuehn, 1982
Cladoceran, Daphnia magna	24	1430	EC_{100}, immobilization	Bringmann and Kuehn, 1982
Cladoceran, Daphnia magna	48	700	no observed mortality	Slooff et al., 1983
Cladoceran, Daphnia magna	48	1080	LC_{50}	Slooff et al., 1983
Cladoceran, Daphnia magna	48	1130-1755	LC_{50}	Canton and Adema, 1978
Cladoceran, Daphnia pulex	48	575	LC_{50}	Canton and Adema, 1978
Cladoceran, Daphnia pulex	48	265	no observed mortality	Slooff et al., 1983
Cladoceran, Daphnia cucullata	48	2470	LC_{50}	Canton and Adema, 1978
Anostracan, Artemia salina	24	831.8	EC_{50}, immobilization	Foster and Tullis, 1985
Isopod, Asellus aquaticus	48	220	LC_{50}	Slooff, 1983
Amphipod, Gammarus pulex	48	182	LC_{50}	Slooff, 1983

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TABLE 6-3 (cont.)

Species	Duration (hours)	Concentration (mg/l)	Response	Reference
		MISCELLANEOUS INVERTEBRATES		
Flatworm, Dugesia lugubris	48	1900	LC_{50}	Slooff, 1983
Oligochaete, Tubificidae	48	1300	LC_{50}	Slooff, 1983
Leech, Erpobdella octoculata	48	2400	LC_{50}	Slooff, 1983
Snail, Lymnaea stagnalis	48	250	no observed mortality	Slooff et al., 1983
Snail, Lymnaea stagnalis	48	350	LC_{50}	Slooff et al., 1983
Hydra, Hydra oligactis	48	940	no observed mortality	Slooff et al., 1983
Hydra, Hydra oligactis	48	1150	LC_{50}	Slooff et al., 1983

NR = Not reported

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6.2. CHRONIC

Gorbi (1984) reported that exposure to 100 mg/ℓ for 25 days caused some mortality and completely inhibited reproduction of Daphnia magna. Other data regarding the chronic toxicity of pyridine to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

The limited information concerning the effects of pyridine on aquatic plant species is summarized in Table 6-4. The blue-green alga, Microcyctis aeruginosa, is the most sensitive of the species tested, with a threshold concentration of 28 mg/ℓ for inhibition of cell multiplication (Bringmann and Kuehn, 1978).

6.4. RESIDUES

Pertinent data regarding pyridine residues in aquatic biota could not be located in the available literature as cited in the Appendix. Jori et al. (1983) stated that pyridine would, theoretically, not be expected to be bioaccumulated to a great extent, because of its relatively low K_{ow}. Verschueren (1977) reported that a concentration of 5 mg/ℓ imparted a bad taste to carp, Cyprinus carpio. Connell and Miller (1981) estimated that the threshold concentration of pyridine in water that could cause tainting of fish and other aquatic organisms was 5-28 mg/ℓ. In the amphibian, Xenopus laevis, 10 or 50 mg/ℓ pyridine resulted in an increased incidence of abnormal embryos (Dumont et al., 1979). Among the invertebrate species tested, the flagellate protozoans, Entosiphon subcatum and Chilomonas paramecium, were the most sensitive, with toxicity thresholds of 3.5 and 3.9 mg/ℓ, respectively (Bringmann and Kuehn, 1980; Slooff et al., 1983), and were also the most sensitive of all aquatic species tested. LC_{50} values for seven insect species ranged from 30-410 mg/ℓ. Cladocerous were

TABLE 6-4

Summary of Data Concerning Acute Toxicity of Pyridine to Aquatic Plants and Bacteria

Species	Concentration (mg/ℓ)	Response	Reference
		ALGAE	
Scenedesmus quadricauda	120	toxicity threshold, cell multiplication inhibition	Bringmann and Kuehn, 1980
Scenedesmus pannonicus	120	toxicity threshold, cell multiplication inhibition	Slooff et al., 1983
Scenedesmus pannonicus	280	48-hour NOEC	Slooff et al., 1983
Selenastrum capricornutum	10	^{14}C fixation was 67% of control value	Giddings, 1979
Selenastrum capricornutum	100	^{14}C fixation was 86% of control value	Giddings, 1979
Selenastrum capricornutum	1000	^{14}C fixation was 80% of control value	Giddings, 1979
Selenastrum capricornutum	50	48-hour NOEC	Slooff et al., 1983
Chlorella pyrenoidosa	150	48-hour NOEC	Slooff et al., 1983

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TABLE 6-4 (cont.)

Species	Concentration (mg/ℓ)	Response	Reference
		BLUE-GREEN ALGAE	
Microcystis aeruginosa	28	toxicity threshold, cell multiplication inhibition	Bringmann and Kuehn, 1978
		BACTERIA	
Pseudomonas putida	340	toxicity threshold, cell multiplication inhibition	Bringmann and Kuehn, 1980
Pseudomonas fluorescens	3000	inhibition of cell multiplication	Spandowska et al., 1973
	100	inhibition of carbohydrate decomposition	
Escherichia coli	2000-8000	inhibition of cell multiplication	Spandowska et al., 1973
	500	inhibition of carbohydrate decomposition	

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somewhat more resistant, with LC_{50} values of 240-2470 mg/ℓ for three Daphnia species (Bringmann and Kuehn, 1977; Canton and Adema, 1978). The most sensitive plant species tested was the blue-green alga, Microcystis aeruginosa, with a toxicity threshold of 28 mg/ℓ (Bringmann and Kuehn, 1978).

6.5. SUMMARY

Although there is a reasonable body of data concerning acute toxicity of pyridine, there is no information about chronic toxicity or accumulation of pyridine in aquatic organisms. The most sensitive fish species tested was carp, which had a 96-hour LC_{50} value of 26.0 mg/ℓ (Rao et al., 1975).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

A TLV of 5 ppm (~15 mg/m³) and a STEL of 10 ppm (~30 mg/m³) have been adopted for pyridine (ACGIH, 1985). The TLV and STEL were considered to be below the level that causes systemic toxicity if skin absorption is prevented (ACGIH, 1980). The values were based on the findings of Smyth (1956) that exposure to 10 ppm may result in mild symptoms and Teisinger (1948) that concentrations of 6-12 ppm (19-39 mg/m³) may cause mild CNS injury. The TLV is above the odor threshold (ACGIH, 1980). The OSHA (1985) permissible exposure limit is also 5 ppm (~15 mg/m³).

7.2. AQUATIC

Hann and Jensen (1977) grouped pyridine as a class 1 compound, i.e., one having 96-hour LC_{50} values in the range of 100-1000 mg/ℓ. Mosevich et al. (1976) reported that in the USSR, the maximum permissible concentration of pyridine that would be harmless to aquatic organisms was 0.01 mg/ℓ.

8. RISK ASSESSMENT

Chronic or subchronic studies on the carcinogenicity of pyridine could not be located in the available literature as cited in the Appendix. The technical report of a chronic gavage study in rats and mice is not yet available (NTP, 1985). No evidence of carcinogenicity was found in rats and mice administered pyridine in subcutaneous and intravenous studies (Mason, 1969; Mason et al., 1971; Homburger, 1968; Derse, 1969).

Pyridine was found to be nonmutagenic when tested for reverse mutation with and without metabolic activation in four strains of Salmonella typhimurium and one strain of Escherichia coli (Florin et al., 1980; Burrell et al., 1983; Riebe et al., 1982; Pai et al., 1978). Pyridine was also negative in a rec assay in E. coli (Riebe et al., 1982). Pyridine increased the frequency of SCE, but not chromosome aberrations, in Chinese hamster cells (Abe and Sasaki, 1977; Ishidate and Odashima, 1977).

One limited study was located on the effect of pyridine on reproduction and teratology. Landauer and Salam (1974) treated chicken eggs with 20 mg pyridine/egg at 96 hours of incubation and found muscular hyperplasia of the legs and occasional abnormalities of the facial skeleton and neck vertebrae in the chicks.

Chronic oral toxicity studies could not be located in the available literature as cited in the Appendix. Several studies have evaluated the toxicity of dietary pyridine to young rats; however, these studies were conducted for 1-4 months and many of the rats died during the first few weeks of treatment (Baxter, 1946, 1948; Baxter and Mason, 1947; Hove, 1953; Coulson and Brazda, 1948). The results however, consistently support a hepatotoxic effect of pyridine. Dietary levels of pyridine in these studies

ranged from 1000-10,000 ppm. Assuming that young rats in a subchronic study consume a daily amount of food equal to 10% of the body weight (Mitruka et al., 1976), the dosage of pyridine would be 100-1200 mg/kg/day. Most animals died in the first 2-3 weeks of treatment; hepatomegaly, liver necrosis cirrhosis and degeneration of the renal tubular epithelium were consistently reported (Baxter, 1946, 1948; Baxter and Mason, 1947; Coulson and Brazda, 1948; Hove, 1953).

Mice treated with pyridine by gavage, 5 days/week for 13 weeks had dose-related decreased body weight gain (males) at $\geq$25 mg/kg and dose-related increased incidence of liver lesions at levels $\geq$100 mg/kg/day. Livers of mice treated at doses $\leq$50 mg/kg/day were not examined microscopically. Deaths occurred in 1/10 and 6/10 males treated with pyridine at 200 and 400 mg/kg/day, respectively. Rats similarly treated with pyridine had reduced body weight gain at doses $\geq$12.5 mg/kg/day (lowest dose tested) and dose-related increased incidence of liver lesions at levels $\geq$50 mg/kg/day. In addition, high-dose rats had increased incidences of interstitial myocarditis and glomerulonephritis compared with controls. Death occurred in 1/10 males at 100 and 200 mg/kg/day levels and in 2/10 females treated with pyridine at 200 mg/kg/day (GSRI, 1979).

Inhalation exposure of rats to 10 or 50 ppm (32 or 162 mg/m^3) of pyridine vapor for 7 hours/day, 5 days/week for 6 months resulted in increased relative liver weight, but had no effect on growth rate or mortality (Encyclopedia of Occupational Safety and Health, 1983).

Toxic effects such as headaches, nervousness, sleeplessness, nausea and vomiting have been reported in humans from occupational exposure to 20-42 ppm (65-136 mg/m^3) (Teisinger, 1948). Pollock et al. (1943) reported similar symptoms in five epileptic humans given pyridine orally at 0.30-1.51

g/day. When the dosage was increased to 1.81 g/day, renal insufficiency and evidence of altered hepatic function occurred. At a dose of 2.41 g pyridine/day, death from hepatorenal failure was reported. Despite the lack of adequate long-term studies, pyridine does appear to be hepatotoxic. Pyridine has been tested by NTP, but the report is not yet available (NTP, 1985). The results of this study may provide some pertinent information about chronic systemic toxicity as well as carcinogenicity.

Since data are insufficient at this time to conclude that pyridine is carcinogenic, it is appropriate to derive an ADI based on toxicity data. The subchronic dietary studies (Baxter, 1946, 1948; Baxter and Mason, 1947; Coulson and Brazda, 1948; Hove, 1958) can be used for the derivation of an ADI because frank effects (death, cirrhosis) were reported at all dose levels tested. An ADI could be derived from the preliminary results of the subchronic gavage study in rats and mice (GSRI, 1979; Kovatch, 1979); however, these results have not been peer-reviewed by NTP. However, using this data a NOAEL for rats of 25 mg/kg/day and a LOAEL of 50 mg/kg/day could be derived. Using this NOAEL and applying an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for extrapolation of subchronic to chronic exposure and 10 to protect sensitive individuals), an ADI of 0.025 mg/kg/day could be derived. However, a provisional ADI of 0.002 mg/kg/day has been recommended by the U.S. EPA (1985) by an inhalation study described in the Encyclopedia of Occupational Health and Safety (1983). In this study rats were exposed to 10 or 50 ppm (32.35 or 161.75 mg/m^3) of pyridine vapor for 7 hours/day, 5 days/week for 6 months.

The lower exposure level of 10 ppm (32.35 mg/m^3) was designated an animal LOEL based on an increased incidence in relative liver weight.

Assuming that a rat breathes a volume of air equivalent to 0.223 m^3/day, absorbs 50% of the inhaled pyridine and weighs 0.35 kg, and converting to continuous exposure by multiplying by 5/7 and 7/24, the transformed dose is 2.15 mg/kg/day. An uncertainty factor of 100 was used to account for inter-species extrapolation and the range of sensitivity of humans to xenobiotics. An additional uncertainty factor of 10 was applied to account for the use of a LOEL instead of a NOAEL. Applying the uncertainty factor of 1000 as described, the ADI for pyridine is 0.002 mg/kg/day or 0.2 mg/day for a 70 kg human. This ADI is sufficiently lower than ADI that could be derived from the TLV of 5 ppm (~15 mg/m^3):

$$15\ mg/m^3 \times 10\ m^3/day \times 5/7 \times 0.5 \div 10 = 5\ mg/day$$

and an order of magnitude lower than the ADI derived from the subchronic rat gavage studies. Because of continuing concern for reported adverse neurotoxic effects associated with short-term low level (6 ppm) occupational exposure (Teisinger, 1948), the extra margin of safety provided by the ADI derived from the rat inhalation data is recommended.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING ON CHRONIC TOXICITY

The toxicity of pyridine was discussed in Section 5.5. and the available studies are summarized in Table 9-1. The equivalent human doses were calculated by multiplying the animal doses by the cube root of the ratio of the animal body weight to the human body weight (70 kg). For human studies, the doses in mg/day were divided by 70 kg for comparison purposes.

Pollock et al. (1943) reported several cases of epileptic patients that were treated orally with pyridine. The case reports cannot be used for RQ determination because these patients were also taking other medications such as sodium bromide, phenobarbital and dilantin sodium. The possibility of an interactive effect of these other medications cannot be precluded. Furthermore, the treatments were short-term and intermittent.

As seen from Table 9-1, the most severe effect of pyridine exposure was early mortality. The lowest equivalent dose at which early mortality was observed was 11.3 mg/kg/day in rats (Baxter, 1946, 1948) and mice (GSRI, 1979). Since the mice in the GSRI (1979) study had a greater survival time, these data will be used to calculate a CS (Table 9-2). Because the study was subchronic, it is necessary to divide the dose by an uncertainty factor of 10, which results in an approximate chronic exposure dose of 1.13 mg/kg/day. Multiplying this dose by 70 kg results in an MED of 79.1 mg/day, which corresponds to an RV_d of 2.7. The RV_e of mortality is 10. Multiplying the RV_d by the RV_e results in a CS of 27, which corresponds to an RQ of 100.

Severe liver lesions, such as cirrhosis, and mycarditis and glomerulonephrtis, which would warrant RV_es of 8, were observed in rats at equivalent doses of $\geq$20.3 mg/kg/day (GSRI, 1979; Kovatch, 1979). These lesions,

TABLE 9-1

Toxicity Summary for Pyridine

Route	Species/ Strain	Sex	Number at Start	Average Weight	Vehicle/ Physical State	Compound and/or Purity	Exposure	Transformed Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	rat/NR	M,F	35/sex/ group	weanling[a]	diet	redistilled pyridine	28 days 0.6% (6000 ppm)	600[b]	67.6	Majority of animals died within 2 weeks. Hepatomegaly, hepatic necrosis, renal damage	Coulson and Brazda, 1948
Oral	rat/NR	M	6/group	weanling[a]	diet	redistilled pyridine	0.1% 1000 ppm	100[b]	11.3	Body weight loss, majority died in 2-4 weeks; acute necrosis and cirrhosis of the liver, renal tubular injury	Baxter, 1946; Baxter and Mason, 1947
Oral	rat/NR	M	6/group	weanling[a]	diet	pyridine citrate	equivalent to 0.1% pyridine	100[b]	11.3	Same as above	Same as above
Oral	rat/ Sprague-Dawley	M	unclear	weanling[a]	diet	pyridine citrate	4 months, 0.34% pyridine citrate (0.1% pyridine) 0.7% pyridine citrate (0.2% pyridine) 1% pyridine citrate (3% pyridine)	100[b]	11.3	>50% of animals died in 1 week; majority of animals died in 2-3 weeks; hepatomegaly; hepatic necrosis; renal degeneration of tubular epithelium	Baxter, 1948
								200[b]	22.6		
								300[b]	33.8		
Oral	rat/ Sprague-Dawley	NR	20	weanling[a]	diet/NR	pyridine	1% pyridine	1000[b]	112.6	75% mortality (15/20) in 11 days; hepatic damage	Hove, 1953

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TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight	Vehicle/ Physical State	Compound and/or Purity	Exposure	Transformed Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	rat/F344	M,F	10/sex/ group	~0.3 (M)[c] ~0.2 (F)[c]	water	97.5%	12.5, 25, 50, 100 or 200 mg/ kg/day, 5 days/ week for 13 weeks	9 18 36 71 143	1.5 (M), 1.3 (F) 2.9 (M), 2.6 (F) 5.8 (M), 5.1 (F) 11.5 (M), 10.1 (F) 23.2 (M), 20.3 (F)	Decreased body weight gain at ≥12.5 mg/kg/day (females) and ≥50 mg/kg/day (males); deaths at ≥100 mg/kg/day; histopathologic lesions in the liver; inflammation, fibrosis and bile stasis in 50 mg/kg/ day females; necrosis cirrhosis in males and females at ≥100 mg/kg/day; myocarditis and glomerulonephritis at 200 mg/kg/day	GSRI, 1979; Kovatch, 1979
Oral	mouse/ B6C3F1	M,F	10/sex/ group	~0.035 (M)[c] ~0.026 (F)[c]	water	97.5%	25, 50, 100, 200 or 400 mg/ kg/day, 5 days/ week for 13 weeks	18 36 71 143 286	1.4 (M), 1.3 (F) 2.9 (M), 2.6 (F) 5.6 (M), 5.1 (F) 11.3 (M), 10.3 (F) 22.7 (M), 20.6 (F)	Decreased body weight gain at ≥25 mg/kg/day (males); deaths at ≥200 mg/kg/day (males); histopathological liver lesions (inflammation in 100 mg/kg/ day males and females; fatty metamorphosis and necrosis at ≥200 mg/kg/day in males and females)	GSRI, 1979; Kovatch, 1979
Inhalation	rat/NR	NR	NR	0.35 kg[d]	vapor	pyridine	10 ppm (32 mg/m³), 7 hours/day, 5 days/week for 6 months	4.25[d]	0.74	Increased relative liver weight	Encyclopedia of Occupational Safety and Health, 1983

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TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight	Vehicle/ Physical State	Compound and/or Purity	Exposure	Transformed Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	human	NR	5	70 kg	liquid	pyridine	up to 60 days 0.31-2.46 mL/day	0.30-2.42 g/day[f] (300-2420 mg/day)	4.3-34.6	At 0.30-1.51 g/ day: anorexia, nausea, vomiting, weakness, sleep- lessness, headache and depression. At 1.8 g/day: renal insufficiency, altered hepatic function. At 2.42 g/day hepatorenal failure and death	Pollock, et al., 1943
Occupational	human	NR	7	70 kg	vapor	pyridine	"chronic" 6-12 (19-39 mg/m³)	136-279 mg/day[g]	1.9-4.0	Headache, nervous- ness, sleepless- ness, nausea, vomiting, tempo- rary vertigo	Teisinger, 1948

[a]Average weight of a weanling rat for a short-term study was assumed to be 100 g

[b]Based on data presented by Mitruka et al., 1976, it was assumed that a young rat will eat a quantity of food equal to 10% of its body weight. Therefore, dosages in mg/kg/day were calculated as follows: d = ppm in food x 0.10.

[c]Estimated from data provided by study

[d]Assumed (U.S. EPA, 1985)

[e]Calcuated by expanding the exposure over a 7-day week and 24 hours/day and multiplying by the inhalation rate of a rat (0.223 m³/day) and dividing by 0.35 kg (U.S. EPA, 1980).

[f]Calculated by multiplying the dose in mg/day by the density of pyridine (see Section 1.2.)

[g]Calculated by multiplying the exposure by 10 m³/day and by 5/7.

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TABLE 9-2

Composite Scores for Pyridine

Route	Species	Transformed Dose	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	mouse	143 mg/kg/day	79.1	2.7	Mortality	10	27	100	GSRI, 1979
Oral	rat	36 mg/kg/day	35.7	3.2	Liver fibrosis, bile stasis	8	25.6	100	Kovatch, 1979; GSRI, 1979
Inhalation	rat	4.25 mg/kg/day	5.1	4.4	Increased relative liver weight	4	17.6	1000	Encyclopedia of Occupational Safety and Health, 1983
Occupational	human	136 mg/day	13.6	3.8	Headache, nervousness, sleeplessness, nausea, vomiting and vertigo	7	26.6	100	Teisinger, 1948

*The doses were divided by an uncertainty factor of 10 to approximate chronic exposure.

however, occurred at doses which also caused deaths; therefore, it is not necessary to calculate a CS.

At an equivalent human dose of 5.1 mg/kg/day no mortality occurred; however, severe liver lesions, consisting of fibrosis and bile stasis, were observed in female rats (Kovatch, 1979; GSRI, 1979). Dividing by an uncertainty factor of 10 and multiplying by 70 kg results in an MED of 35.7, which corresponds to an RV_d of 3.2. The lesions warrant an RV_e of 8 since bile stasis represents a definitive organ dysfunction. The CS is 25.6, which corresponds to an RQ of 100.

Decreased body weight gain occurred in rats and mice at equivalent human doses of $\geq$1.3 mg/kg/day (GSRI, 1979); this effect warrants an RV_e of 4. Decreased liver weight, which also warrants an RV_e of 4, was observed at 0.74 mg/kg/day (Encyclopedia of Occupational Safety and Health, 1983). Dividing by 10 and multiplying by 70 kg results in an MED of 5.2 mg/day, which corresponds to an RV_d of 4.4. The CS is 17.6, which corresponds to an RQ of 1000.

The 136 mg/day dose in the "chronic" human occupational exposure report by Teisinger (1948) was also divided by an uncertainty factor of 10 to give an MED of 13.6 mg/day, because the term "chronic" was not further defined. The MED corresponds to an RV_d of 3.8. The effects of headache, nervousness, sleeplessness and temporary vertigo represent neuropathy with noticeable behavioral changes, thereby warranting an RV_e of 7. The CS is 26.6, which corresponds to an RQ of 100. Although the CS obtained from the data in mice for early mortality is slightly higher, the CS obtained from the human study is preferable and is recommended for the basis of the RQ for pyridine (Table 9-3). In a previous determination, U.S. EPA (1983) used the human data of Pollock et al. (1943) as the basis of the RQ of 100. However,

TABLE 9-3

Pyridine

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	occupational
Dose*:	13.6 mg/day
Effect:	headache, nervousness, sleeplessness, nausea, vomiting, vertigo
Reference:	Teisinger, 1948
RV_d:	3.8
RV_e:	7
Composite Score:	26.6
RQ:	100

*Equivalent human dose

the human occupational data of Teisinger (1948) appear to be a more appropriate basis for the RQ, because the results of the Pollock et al. (1943) study were confounded by other medications and because the treatment was short-term and intermittent.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Although pyridine has been tested by gavage in rats and mice in a chronic study, the report of this NTP study is not yet available (NTP, 1985). Other studies by a relevant route could not be located in the available literature; however, several studies in which pyridine was administered parenterally to mice or rats have yielded negative results. Derse (1969) injected neonatal mice (Random-bred, Texas-Yale) subcutaneously with 0.133 or 1.33 mg pyridine/mouse and observed them for 15 months. No significant differences in neoplastic lesions were observed between treated and control mice.

Subcutaneous injection of 0, 3.0, 10.0, 30.0 or 100.0 mg/kg of pyridine in groups of 20-80 F344 male and female rats, 2 times/week for 52 weeks and observed for an additional 6 months did not result in an increased incidence of tumors compared with controls, although sarcomas developed at the injection site in 1-2% of both treated and control rats (Mason et al., 1971; Homburger (1968) injected 100 male C57BL/6 mice (7 weeks old) subcutaneously with 6 mg pyridine/mouse. Five weeks later, tissue from the injection site was injected into 25 mice serving as secondary hosts. No evidence of a carcinogenic effect was observed. In a pulmonary adenoma assay, groups of 50 CF1 female mice and 50 A/Jax female mice received a single intravenous dose of 6.0 mg pyridine/mouse (Homburger, 1968). Another group of 20 CF1 female mice received seven injections at monthly intervals of 6.0 mg/mouse/injection. The mice were killed at 28 weeks after the single or the last

repeated dose. No significant increased incidence of pulmonary adenomas was observed compared with controls. In another experiment, Homburger (1968) injected 50 male C57B1/6 mice subcutaneously with dibenzpyrene. Pyridine at 6 mg/mouse/injection was injected 24 hours, 7 and 14 days later, and the mice were killed 29-31 weeks after the start of the experiment. The results of the co-carcinogenicity study were inconclusive.

No data regarding the carcinogenicity of pyridine to humans were available. Until the report of the NTP study becomes available, pyridine must be regarded as an IARC Group 3 and an EPA Group D chemical (U.S. EPA, 1984).

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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